Potential Role of Stress and Sensitization in the Development and Expression of Multiple Chemical Sensitivity

Barbara A. Sorg and Balakrishna M. Prasad

Program in Neuroscience, Department of Veterinary and Comparative Anatomy, Pharmacology and Physiology, Washington State University, Pullman, Washington

Chemical sensitivity in humans may be an acquired disorder in which individuals become increasingly sensitive to chemicals in the environment. It is hypothesized that in individuals with multiple chemical sensitivity (MCS), a sensitization process has occurred that is akin to behavioral sensitization and kindling observed in rodents. In the rodent sensitization model, repeated exposure to stress or drugs of abuse enhances behavioral and neurochemical responses to subsequent stimuli (stress or drugs of abuse). Kindling is a form of sensitization in which repeated application of electrical stimuli applied to the brain at low levels culminates in the induction of full-blown seizures when the same stimulus is applied at a later time. A similar sensitization of specific limbic pathways in the brain may occur in individuals with MCS. The time-dependent nature of sensitization and kindling and the role of stress in the development of sensitization are discussed in the context of rodent models, with an emphasis on application of these models to human studies of MCS. — Environ Health Perspect 105(Suppl 2):467–471 (1997)

Key words: multiple chemical sensitivity, kindling, limbic system, sensitization, stress

Introduction

Chemical sensitivity is an ill-defined disorder occurring in a subset of the human population that has been attributed to exposure to chemicals, usually volatile organic compounds. Individuals who develop sensitivity to chemicals report an array of symptoms involving the central nervous system (CNS) and other organ systems; among the symptoms are fatigue, depression, headaches, gastrointestinal problems, muscle and joint pain, irritability, memory and concentration difficulties, and many others (*1,2*). Although a case definition for chemical sensitivities, often referred to as multiple chemical sensitivity or MCS, has not been agreed upon, a common feature of chemical sensitivity is found among individuals experiencing symptoms as a result of exposures at various sites. Such individuals include Gulf War veterans (Gulf War syndrome), industrial workers, and those living near hazardous waste sites. MCS is purported to occur after single, high-dose exposures (such as chemical spills) or repeated low-level exposures to chemicals (*1*).The existence of MCS has aroused much controversy which stems largely from several factors: the inability to rigorously identify true sensitivities to chemicals because of the unreliability of self-reports linking illness to chemical exposure; the diversity of symptoms and their overlap with those of other illnesses, such as somatoform disorder, chronic fatigue syndrome, fibromyalgia, panic disorder, and posttraumatic stress disorder (PTSD); and the possibility of falsely attributing symptoms from other illnesses to chemical exposure (*3–9*). Typically, individuals with MCS complain of ill effects from chemicals present in very low concentrations in the environment, suggesting that a possible amplification has occurred in the processes involved with either the perception of illness from chemicals or other effects of these compounds on the system.

Identification of potential triggering mechanisms in the development of this disorder is critical to a greater understanding of MCS. Since MCS appears to develop because of exposure to a wide variety of chemicals, it is likely that MCS is a result of a common neurological disorder rather than a manifestation of distinct pathologies specific to each chemical. The limbic system integrates environmental stimuli into behavioral output, and may be responsible for the wide array of symptoms reported by individuals with MCS. Bell et al. (*10*) have proposed that MCS symptoms result from a sensitization process occurring in specific limbic regions of the CNS and hypothesize that limbic kindling and/or sensitization in rodents may provide an appropriate model system for MCS studies. Several features of sensitization appear to parallel those of MCS, including the progressive increase in sensitivity to drugs and chemicals (*10,11*), the apparent permanence of sensitivity (*1,12*), the greater sensitivity of females than males (*13,14*), and the spreading of sensitization in response to stimuli other than the initial stimulus used to induce sensitization (as with cross-sensitization between psychostimulants and stress) (*14,15*). This paper addresses the potential involvement of stress and temporal changes in the development of MCS with analogies to behavioral sensitization and kindling in rodents.

Sensitization/Kindling

Sensitization in rodents refers to the progressive and enduring increase in behavioral (usually locomotion or stereotyped movements) or neurochemical responses after repeated exposure to stress or drugs of abuse. Sensitization in rodents serves as an animal model for drug-induced psychosis, panic disorder, and PTSD. Kindling is a form of sensitization in which repeatedly presented electrical stimuli to the brain (usually the amygdala) that initially do not produce seizures can, with the passage of time, produce full-blown seizures in response to the same level of stimulus (*16*).

Both behavioral sensitization by psychostimulants or stress and kindling result in increased responsiveness of the organism to stimuli with the passage of time. Although kindling is described as a subtype of sensitization in the general sense, the relationship between behavioral sensitization induced by psychostimulants or stress and electrical kindling is unclear. There is much evidence

This paper is based on a presentation at the Conference on Experimental Approaches to Chemical Sensitivity held 20–22 September 1995 in Princeton, New Jersey. Manuscript received at EHP 6 March 1996; manuscript accepted 21 October 1996.

This research was supported by the Wallace Research Foundation.

Address correspondence to Dr. B.A. Sorg, Department of VCAPP, Stadium Way, Wegner, Room 205, Washington State University, Pullman, WA 99164-6520. Telephone: (509) 335-4709. Fax: (509) 335-4650. E-mail: barbsorg@vetmed.wsu.edu

Abbreviations used: CNS, central nervous system; CRH, corticotropin-releasing hormone; MCS, multiple chemical sensitivity; NMDA, *N*-methyl-D-aspartate; PTSD, posttraumatic stress disorder.

for a cocaine kindling phenomenon in which seizures induced by cocaine are observed with increased frequency in animals administered cocaine repeatedly (*17*). To determine if electrically induced kindling and psychostimulant-induced sensitization share common neural substrates, repeated psychostimulants have been administered and subsequent effects on the kindling process examined. Some studies have failed to find any effects of drug pretreatment on kindling (*18,19*), whereas repeated methamphetamine has been reported to lower the seizure threshold (*20*). The anticonvulsant, carbamazepine, which blocks electrical kindling once established (*21*), also decreases the development of cocaine-kindled seizures but does not block the development of behavioral sensitization to cocaine (*22*). More recently, Schenk and Snow (*23*) conducted an experiment to address the converse question of whether electrical kindling potentiated the effect of cocaine-induced locomotor activity. Electrical kindling of the medial prefrontal cortex (limbic cortex), but not the hippocampus, produced behavioral sensitization to cocaine. Thus, differing effects may be obtained depending on which brain region has been electrically stimulated. Additional studies suggest that one potential overlap between cocaine sensitization, cocaine-kindling, and electrical kindling occurs at the *N*-methyl-D-aspartate (NMDA) glutamate receptor subtype (*21,24,25*).

Role of Stress in Sensitization/Kindling and MCS

The effects of stress on human health have been apparent for several years (*26*). However, whether life stressors can render an individual more susceptible to develop illnesses from chemical exposures and ultimately produce MCS is unknown. Bell et al. (*27*) have shown that stress may be a factor contributing to the onset of MCS. Symptoms of MCS involve several systems, including the autonomic, immune and endocrine systems (*28*), which can be modulated by stress. Because the brain regulates endocrine, autonomic, and immune system function, stress effects on the CNS must be considered potential predisposing factors to MCS.

Stress has a great impact on the development and expression of behavioral sensitization in rodents. Sensitization studies over the past 15 years have described a cross-sensitization of stress and drugs of abuse (*15*). In such a cross-sensitization paradigm, repeated stress is administered to rodents, resulting in augmentation of behavioral and neurochemical measures in response to subsequent drug exposure. Thus, environmental stress can replace repeated psychostimulant administration, altering the same pathways utilized for expressing sensitization.

The role of environmental stress in enhancing susceptibility to kindling or vice-versa is unclear at present. The increase in anxiety levels produced by amygdala kindling (*29*) can be reversed by an environmental stressor (saline injection) or by corticotropin-releasing hormone (CRH), a stress-induced hormone (*30*), suggesting that anxiety induced by kindling can be countered by stress. On the other hand, additional studies have examined whether CRH or glucocorticoids, both of which increase after stressful stimuli, alter the course of electrical kindling. Cocaine kindling is enhanced by CRH administration (*31*), and glucocorticoids enhance CRH-induced seizures (*32*). Other stressors such as prenatal stress and social conflict indicate a complex relation between stress and seizure activity. The effect of prenatal stress on convulsant drug-induced seizures depends on the developmental stage during which stress is applied (*33*). The development of the kindling process has been shown to be altered differently by the outcome of conflict stress, i.e., whether the conflict resulted in victory or defeat (*34*). When all the studies to date regarding the neural substrates involved in psychostimulant/stress-induced sensitization and kindling are considered, there appears to be some overlap. Additional studies examining the effects of chemicals using animal models are necessary to determine if one or both of these models best describe the mechanisms mediating the onset and/or progression of chemical sensitivity in humans.

In addition to the influence of environmental factors such as stress, it is likely that genetic factors may predispose individuals to develop MCS. The suggestion that chronic stress may be a predisposing factor in MCS allows one to speculate that MCS onset in relatively stress-free individuals is due to existing alterations in those specific pathways affected by chronic stress. For example, the expression of a vast array of genes in the CNS is altered by exposure to chronic stress (*35*). Individuals who may have genetic predispositions to develop MCS could exhibit similar alterations in one or many of the genes normally expressed only after chronic stress. Thus, adaptive responses to further stress (including chemicals) become maladaptive for the organism because of a previous state of altered gene expression.

Time-dependence of Sensitization/Kindling

In individuals with MCS, chemicals are believed to be the initiating (often referred to as triggering) stimuli that after the passage of time produce a wide array of symptoms when the same or often a different and unrelated chemical is presented (referred to as elicitation). Most reports indicate that the onset of MCS occurs long after initial chemical exposure (often several weeks or months), suggesting that time-dependent mechanisms are involved in this process. In behavioral sensitization and kindling studies, the effects of repeated drug or electrical stimuli presentation also progressively increase with the passage of time. Recent studies on behavioral sensitization indicate a clear temporal and anatomical distinction between events involved in initiation compared with those involved in elicitation, or expression, of sensitization (*36*). These studies indicate that a number of transient changes occur in the midbrain during the initiation phase of sensitization; these changes disappear by the time expression of sensitization is observed. These transient changes are thought to trigger permanent alterations in the forebrain that are responsible for the expression of sensitization. Similarly, various stages of kindling are associated with activation of the immediate-early gene, c-*fos*, in different brain regions depending on the stage of kindling (*37*). The concept that different phases of sensitization and kindling exist is underscored by the differential responsiveness to pharmacological manipulations during each phase. For example, blocking of the D2 dopamine receptor subtype prevents conditioned behavioral sensitization to cocaine if the cocaine is given during the initiation phase; that is, just prior to each daily drug injection. However, after initiation events have been allowed to take place in the absence of this antagonist, the expression phase of sensitization cannot be prevented by D2 dopamine receptor blockade (*38*). The different phases of kindling also respond differentially to drugs (*39*).

These studies indicate that, as with progressive chronic illnesses, there are discrete stages through which the organism advances as a consequence of several different biochemical/molecular changes (*39*). The notion that many of these changes are likely to be transient further complicates the task of determining physiological end points that may serve as diagnostic criteria for MCS. As a first step toward understanding the events that follow the triggering of MCS, it is important to identify individuals exposed to a particular chemical environment who are synchronized in their initiation of MCS. Longitudinal studies on workers involved in a chemical spill or installment of new carpeting in a building would serve as logical first steps toward understanding the MCS phenomenon. Long-term continued follow-up investigations should identify alterations in physiological changes in all exposed individuals (those who do and those who do not develop MCS symptoms). Follow-up studies of non-MCS individuals experiencing the same high-level, short-term chemical exposures would provide the control group with which to compare changes reported by those who develop MCS symptoms. The list of physiological parameters that could be assessed includes but is not limited to the following: changes in heart rate and respiration, alterations in neuroendocrine, electroencephalography and electromyography patterns, and a battery of neuropsychological tests for memory and attention (*10,40,41*). Through several testing procedures, a pattern of changes may emerge in individuals who develop chemical sensitivity. Based on several reports, only a subpopulation of exposed individuals would be expected to develop MCS symptoms as a result of chemical exposure (responders), whereas a larger percentage of the population would not exhibit MCS symptoms (nonresponders). It should be emphasized that only the most rigorously executed studies (e.g., those employing double-blind chemical challenges) should be conducted to gain knowledge about consistent changes in the pattern of physiological responses. Moreover, comparison of these patterns with those of similarly chemically exposed individuals in the same workplace setting not reporting chemical sensitivities is critical to identify relevant changes in physiological and neuropsychological function that may accompany MCS. Regular periodic testing of these parameters in all exposed subjects may be imperative to identify pathological changes associated with the initiation and progression of MCS compared with compensatory changes that occur in all exposed individuals. Compensatory changes are considered adaptive responses that bring an individual's system back to homeostasis, whereas pathological changes are those that contribute to the onset of MCS.

Sensitization/Kindling As a Model for MCS

The lack of animal models and treatment strategies for MCS makes it difficult to directly assess the goodness-of-fit between sensitization/kindling phenomena and MCS. However, some studies have demonstrated that many chemicals implicated in inducing MCS symptoms, including pesticides and organic solvents, promote seizures and/or kindling in limbic structures (*42–44*). A potential criticism of using sensitization and kindling models to mimic MCS in humans is that the levels of electrical or drug stimulation exceed those encountered by humans in the environment, especially when considering several reports that suggest that long-term, low-level chemical exposures produce MCS symptoms (*1*). However, recent studies have demonstrated long-term cross-sensitization to the locomotor effects of the dopamine agonist, apomorphine, in rats exposed to subthreshold levels of toluene for 1 month (*45*). Recent data from our laboratory indicate that daily exposure to a low level of formaldehyde (1.0 ppm) for 1 hr per day for 1 week does not induce a cross-sensitization to cocaine-induced locomotion, but the same daily exposure for a 1-month period produces a robust sensitization of rearing behavior in response to cocaine (Sorg et al., unpublished results). These studies suggest that low-level, long-term exposure can sensitize specific limbic pathways. These same pathways long have been thought to be associated with certain human behaviors such as panic disorder and psychoses as well as behavioral responses to rewarding and aversive stimuli. Thus, the data from these animal studies suggest that the potential for altered limbic system functioning in humans exists, whether at the level of amplified perception of chemicals or at other undetermined sites within the CNS.

Since a general definition of sensitization is any increase in a neuronal response to a stimulus, modeling MCS studies after sensitization in animals may prove to be useful, even if the fit is not a perfect one. In spite of the observed similarities between the onset of MCS and sensitization/kindling, these rodent models cannot accurately represent all aspects of MCS. It is not plausible to develop an animal model of MCS based on the wide variety of symptoms experienced by chemically sensitive humans, but a nonhomologous, mechanistically based model may provide clues about alterations in specific brain pathways. Thus, changes in the same neurochemical pathways in animals as in humans do not necessarily translate into similar behavioral manifestations. One example of this is the different behavioral outcomes in rodents and humans following repeated cocaine exposure; in the former, locomotor activity is enhanced, in the latter, psychotic symptoms develop. Both behaviors, however, are believed to be mediated by amplification of limbic dopamine neurotransmission, and both behaviors are blocked by dopamine receptor antagonists. Eventually, treatments that could interfere with the initiation or expression of sensitization and/or kindling in rodents may prove beneficial in the development of treatment strategies for MCS.

Summary and Future Directions

Two major issues should be considered in designing animal and human studies. First, the time-dependent changes that occur in response to a demonstrable chemical exposure should be taken into account. Investigating individuals chemically exposed within a relatively narrow window of time would increase the likelihood of testing individuals who are in similar stages of the progression of MCS. Different underlying physiological and neuropsychological changes that accompany the transformation from early to later stages of MCS may therefore be mapped more accurately. Long-term testing of physiological and neuropsychological parameters should be conducted not only in individuals who develop MCS (responders) but in all exposed individuals (including nonresponders who do not develop MCS symptoms). Measurements should begin at the earliest time possible after a high-level, short-duration exposure.

Second, the role of stress in predisposing individuals to the onset of MCS should be considered. Although self-reports of stress and anxiety can be somewhat unreliable, this should not preclude collection of self-reported levels of previous and current life stressors. Animal studies designed to model MCS should consider the role of repeated stressful stimuli in predisposing the animal to subsequent chemical-induced changes in brain and behavior. For these particular studies, physiological stressors such as swim stress, footshock, tailpinch, sleep or food deprivation, maternal deprivation, and psychological stressors such as conditioned fear, should be administered during various stages of development (prenatal, neonatal, adulthood) to determine if previous stress or stress administered concurrently with chemical exposure predisposes animals to altered CNS function. Such alterations in CNS functioning (*46*) could easily be measured by monitoring behaviors such as sensitization of locomotion/stereotypy to psychostimulants, kindling development, startle response, olfactory threshold, conditioned and nonconditioned avoidance responses to aversive stimuli (including odors), memory tasks, and other complex tasks requiring attention and response sequences. These behavioral measures are designed to assess changes in sensory, motor, memory and cognitive functions. Thus, examination of the effects of repeated chemical exposure in animals on specific behaviors mediated by brain pathways that have already been well mapped provides a starting point for understanding which neural substrates may be altered.

A final point should be made about the use of animal models for a complex disorder such as MCS. Alterations in CNS functioning of animals administered repeated chemical exposure do not formally prove that MCS is a true disorder in humans, but any alterations would lend strong support to the potential for such alterations to take place in the human CNS as well. Such findings would warrant careful attention and further rigorous investigation in humans.

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